0041-1337/96/6107-1038$03.00/0
TRANSPLANTATION

Vol. 61, 1038–1046, No. 7, April 15, 1996
Printed in U.S.A.

RANDOMIZED, PROSPECTIVE TRIAL OF CYCLOSPORINE MONOTHERAPY VERSUS AZATHIOPRINE-PREDNISONE FROM THREE MONTHS AFTER RENAL TRANSPLANTATION[1]

LUKAS B. HILBRANDS,[2] ANDRIES J. HOITSMA, AND ROBERT A.P. KOENE

Department of Medicine, Division of Nephrology, University Hospital Nijmegen, NL-6500 HB Nijmegen, The Netherlands

Cyclosporine (CsA) and prednisone (Pred) are the most widely used drugs for immunosuppression after renal transplantation, but both drugs have marked side effects. Either replacement of CsA by azathioprine (Aza) or withdrawal of prednisone (Pred) resulting in CsA monotherapy can be employed to circumvent the adverse effects in the long run. Both treatment regimens were compared in this prospective randomized trial in patients who were treated with CsA and Pred during the first 3 months after renal transplantation (CsA: n=64, Aza-Pred: n=63, median duration of follow-up: 3.9 years). Estimated graft survival rates at 5 years after transplantation (in patients with a functioning graft at 3 months) were 78% in the CsA group and 87% in the Aza-Pred group. The incidence of a rejection within 3 months after start of steroid withdrawal or conversion from CsA to Aza was 30% and 25%, respectively (NS). At 2 years after transplantation, serum creatinine levels were lower in the Aza-Pred group (126±35 μmol/L) than in the CsA group (180±78 μmol/L; $P<0.001$). There were no differences in blood pressure or incidence of infections between the treatment groups. Treatment-related costs were measured during the first year after transplantation and were lower in the Aza-Pred group (DFL 40,882±18,895 vs. DFL 53,484±44,828; 1 DFL [Dutch guilder] is about US $0.60; $P<0.05$). In conclusion, CsA monotherapy and Aza-Pred treatment from 3 months after renal transplantation are comparably effective immunosuppressive treatment regimens, although Aza-Pred therapy results in better graft function. Withdrawal of steroids and replacement of CsA by Aza both carry a substantial risk of rejection. The previously demonstrated cost effectiveness of CsA-containing therapies seems to be limited to the first phase after transplantation. Conversion to Aza-Pred at 3 months after transplantation reduces costs.

The combination of cyclosporine (CsA*) and prednisone (Pred), frequently supplemented by azathioprine (Aza), is widely used as a standard immunosuppressive drug regimen after renal transplantation. Although data regarding graft survival with the use of these drugs are quite satisfactory, concern remains about their side effects, especially when they are used chronically. Pred is feared for its effects on bone metabolism and skin, its potential to induce hyperglycemia, hyperlipidemia, and cataract, and its contribution to hypertension (*1*, *2*). The nephrotoxic properties of CsA are well known and long-term use of this drug has been associated with irreversible loss of graft function due to vascular obliteration and interstitial fibrosis (*3*), although recent data on this issue are less worrisome (*4*, *5*). In addition, CsA importantly contributes to posttransplant hypertension (*6*) and has also been implicated in the pathogenesis of hypercholesterolemia in these patients (*2*). To reduce the incidence of these long-term adverse effects in patients treated with CsA and Pred, two strategies may be followed. One is to withdraw the steroids, leading to CsA monotherapy. Alternatively, CsA can be replaced by Aza, a drug with a less impressive side effect profile, with continuation of Pred. Conversion from CsA to Aza at 3 months after renal transplantation has been our standard protocol during recent years. In different studies, both CsA monotherapy (*7–9*) and conversion from CsA to Aza (*10-13*) have been demonstrated to yield adequate results in terms of graft survival and graft function. In 1989, we initiated a randomized, prospective trial to compare these two treatment regimens with respect to efficacy, side effects, and costs. All patients were on CsA and Pred until 3 months after transplantation, when they were randomized to CsA monotherapy or Aza-Pred. With a duration of follow-up of at least 2 years in all patients, this article describes the results with emphasis on rejection incidence, graft function, and costs. Detailed data on the effects of both therapies on quality of life (*14*) and lipid metabolism (*15*) during the first year after transplantation are published separately.

PATIENTS AND METHODS

Patient population and randomization procedure. From June 1989 to June 1992, all 236 adult patients who underwent a first or second cadaveric renal transplantation at our institution were candidates for this study. Patients were excluded when they fulfilled one or more of the following exclusion criteria: age above 65 years (n=10), history of psychiatric disease or alcohol abuse (n=14), history of malignancy (n=7), signs of active hepatitis or carriage of hepatitis B surface antigen (n=7), hemolytic uremic syndrome as original kidney disease (n=6), use of antiepileptic drugs (n=5), and allergy to Aza (n=2). Quality of life measurements necessitated the exclusion of patients with poor knowledge of Dutch language (n=16). Finally, five patients refused to participate, bringing the number of patients who were eligible for the study to 185.

Patients received CsA and Pred during the first 3 months after transplantation. Afterward, they were allocated to CsA monotherapy or to the combination of Aza and Pred. Treatment allocation was carried out by the minimization method (*16*) with frequency matching for the following factors: sex and age (≤40 and >40 years) of the recipient, diabetes mellitus (yes/no), type of previous renal replace-

[1] This study was supported by a research grant from Sandoz, Basel, Switzerland.

[2] Address correspondence to: Lukas B. Hilbrands, Department of Medicine and Division of Nephrology, University Hospital Nijmegen, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands.

* Abbreviations: ATG, antithymocyte globulin; Aza, azathioprine; CsA, cyclosporine; Pred, prednisone.

ment therapy (hemodialysis or continuous ambulatory peritoneal dialysis), previous transplantation (yes/no), number of rejection episodes (0, 1, or ≥2), treatment with antithymocyte globulin during the first 3 months (yes/no), temporary interruption of CsA therapy (<10 or ≥10 days), graft function (creatinine clearance <50, 50–75, or >75 ml/min), proteinuria (<0.1, 0.1–1.0, or >1.0 g/L), number of antihypertensive drugs (0, 1, 2, or ≥3), and age of the donor (≤10, 11–50, or ≥51 years). At 3 months after transplantation, 58 of the 185 eligible patients could not be allocated to one of either treatment arm. Main causes were a relatively high incidence of patient death (n=8) and graft loss (n=30), resulting in a graft survival rate of 79% at 3 months after transplantation. Other reasons to withdraw patients from randomization were: loss of patient to follow-up (n=1), contraindication for CsA by clinical judgment (usually because of signs of CsA nephrotoxicity; n=17), use of Aza contraindicated because of bone marrow depression (n=1), and use of Pred contraindicated because of severe osteoporosis (n=1). The remaining 127 patients made up our study population.

Postulating a 2-year graft survival (starting with 100% at 3 months after transplantation) of 80% with our standard therapy, 80 patients on each treatment were required to provide 80% power of detecting a difference in graft survival of 15%. Lower than expected patient accrual and a high incidence of graft loss before randomization resulted in a somewhat fewer number of patients in each group after the 3-year accrual period.

The most frequent causes of renal insufficiency in the study patients were chronic pyelonephritis (n=20), autosomal dominant polycystic kidney disease (n=13), and IgA nephropathy (n=9). Two patients (both in the CsA group) had diabetic nephropathy and in 22 patients the cause of renal failure was unknown.

A prognostic index, a score including information on both the donor and recipient that was developed to predict graft survival, was calculated according to Thorogood et al. (*17*).

Study protocol. The surgical procedure included infusion of mannitol and a moderate hydration protocol, as described previously (*18*). After surgery, CsA was given intravenously (3 mg/kg/day) for the first 3 days, followed by 12 mg/kg/day in two divided oral doses during the first month. This was gradually reduced to 4 mg/kg/day at 3 months after transplantation, with the dosage adjusted to maintain CsA trough blood levels between 200 and 400 ng/ml (monoclonal antibody assay). In case of signs of severe CsA nephrotoxicity, temporary replacement of CsA by Aza (3 mg/kg) was allowed. Prednisolone was given at a dose of 100 mg/day i.v. during the first 2 days, followed by an oral Pred dosage of 25 mg/day during the remainder of the first month and 20 mg/day during the second and third month after transplantation. In patients who were randomized to receive CsA monotherapy, CsA was continued in the same dosage with adjustments to reach trough blood levels between 100 and 200 ng/ml (monoclonal antibody assay). The daily Pred dosage was reduced by 5 mg every 2 weeks, which resulted in CsA monotherapy after 6 weeks. In patients allocated to Aza-Pred therapy, CsA was replaced without overlap by Aza in a dosage of 3 mg/kg. Their Pred dosage was temporarily increased from 20 to 25 mg/day and reduced by 5 mg every 2 weeks until a maintenance dose of 10 mg/day was reached. In the CsA group, Pred was restarted if more than one acute rejection or chronic vascular rejection occurred after randomization. The same conditions led to replacement of Aza by CsA in the Aza-Pred group. In case of severe and persistent side effects, attributable to one of the drugs, patients were put on the alternative treatment regimen.

The diagnosis of acute rejection was made on clinical grounds and histologically confirmed in 81% of cases. During the first 3 months after transplantation, acute rejection episodes were treated with methylprednisolone (1 g/day i.v. on 3 consecutive days) or antithymocyte globulin (ATG, RIVM Bilthoven, The Netherlands; 200 mg/day i.v. on alternate days for 10 days). An oral course of high-dose Pred (initial dosage 200 mg/day tapered to 25 mg/day in 12 days) was given after failure of one or both of these treatments. From 3 months after transplantation (i.e., after randomization), acute rejection episodes were treated primarily with ATG in all cases. High-dose Pred courses were given in case of failure of ATG, bone marrow suppression, or previous treatment with ATG for rejection. Occasionally, acute rejection episodes were treated with monoclonal anti-CD3 antibodies.

Hypertension, defined as diastolic blood pressure above 95 mmHg on three consecutive occasions, was initially treated in a standard way using a β-blocker (atenolol), followed by the addition of a calcium-antagonist (nifedipine) and a diuretic (chlorthalidone) when necessary. Beyond the first year after transplantation, when most patients were seen in different community hospitals, antihypertensive therapy reflected local practice.

Body weight and blood pressure as well as results from routine clinical chemistry were recorded at regular intervals as part of the usual posttransplant patient evaluation. A diagnosis of urinary tract infection was made when a positive urine culture prompted antibiotic therapy. Cytomegalovirus infection was defined by a 4-fold rise in IgG antibody titer. The diagnosis of other infections was based on clinical judgment. Creatinine clearance was estimated with the formula given by Cockcroft and Gault (*19*). Proteinuria was defined as urinary protein concentration of 0.2 g/L or more (24-hr urinary protein excretion was not measured routinely). Whole blood CsA levels were measured with a fluorescence polarization immunoassay (Abbott Laboratories, North Chicago, IL), initially using polyclonal antibodies directed against the parent molecule of CsA and some of its metabolites. The majority of blood levels were measured with a modified kit, using monoclonal antibodies against the CsA parent molecule without cross-reactivity. A conversion factor of 0.5 was used to adjust the initial values to those currently measured.

The study was approved by the hospital ethics committee and all patients gave written informed consent.

Cost analysis. The health care costs directly related to either treatment regimen were calculated for the first year after transplantation. Costs of kidney acquisition and indirect costs to society, e.g., costs related to disablement, were not considered. Two patients who died, two patients with graft loss, and one patient in whom insufficient data were available were excluded from this analysis (death and graft loss were evenly distributed among both groups). The medical records were used as a data source for number of admission days, number of visits to the outpatient clinic, and amounts of all drugs that were used during hospital stays (except drugs used in the operating room) as well as on an outpatient basis. Similarly, the number of blood products administered and the number of CsA blood level measurements were counted. Our hospital financial administration service provided data on activities regarding the following items: clinical laboratory, operating room and anesthesia, diagnostic radiology, nuclear medicine, endoscopy, pathology, and physiotherapy. Prices current during 1993 or 1994, and expressed in Dutch guilders (1 DFL is about US $0.60) were used to calculate costs. The direct costs of hospital days and visits to the outpatient clinic were estimated on the basis of personnel costs and material expenses (excluding medication and blood products) and amounted to about DFL 300 and DFL 75, respectively. For the intensive care unit, costs were estimated at DFL 2000 per day. The costs of other services were assessed in an analogous way, and when reliable estimations were not attainable (as for laboratory services), charges were used as a proxy for costs.

Statistical analysis. The results were analyzed on an intention-to-treat basis. Calculations were performed with the SAS system (SAS Institute Inc., Cary, NC). Data are given as means with SD unless stated otherwise. Unpaired and paired comparisons of numerical data were performed with Wilcoxon's rank sum and signed ranks tests. Proportions were compared with chi-square analysis using continuity correction or with McNemar's test when appropriate. Probabilities of survival were calculated using the Kaplan-Meier product limit method and for comparison of survival curves the log rank test was used. A *P*-value smaller than 0.05 was considered statistically significant.

RESULTS

The characteristics of patients and their kidney donors are given in Table 1. Except for a better degree of HLA-B matching in the Aza-Pred group, there were no significant differences between the treatment groups. In addition, the 58 patients who initially were eligible for the study but could not be randomized at 3 months after transplantation did not differ with regard to these baseline characteristics. At the time of randomization, there were no differences between groups in regard to clinical data (Table 1). The median duration of follow-up in patients with still-functioning grafts was 3.9 years (range: 2.7–5.6 years).

Course of treatment. Since the originally assigned treatment was changed for various reasons in a considerable number of patients, an overview of the course of treatment in all randomized patients is given in Table 2. In some patients, the immunosuppressive treatment regimen had to be changed for a second or third time. Despite the numerous changes, all data were analyzed according to the intention-to-treat principle. In patients who died or in whom graft failure occurred (n=21), therapy had been changed previously in seven cases. Persistent symptoms of a steroid withdrawal syndrome (fatigue, arthralgia) necessitated temporary reinstitution of steroids in three CsA-treated patients, but eventually these patients received CsA monotherapy. In the CsA group, the CsA dose gradually decreased from 4.0±1.0 mg/kg/day at the end of the first year to 2.9±0.9 mg/kg/day at the end of the fifth year after transplantation. Only CsA trough levels that were measured during the first 9 months after allocation to CsA monotherapy were analyzed, since beyond this period most of the patients were seen in various community hospitals, which used different analytical techniques to determine CsA levels. The frequency of levels below the target range varied from 2% at 5 months after transplantation to 7% at 4 months after transplantation.

Patient and graft survival. Estimated 5-year patient survival rates (in survivors at 3 months) were 92% and 95% in the CsA and Aza-Pred group, respectively. The death of six patients in the CsA group was caused by pneumonia (n=3, caused by *Pneumocystis carinii* in one case), myocardial infarction (n=1), rupture of abdominal aortic aneurysm (n=1), and uterine cervix carcinoma (n=1). In the Aza-Pred group, three patients died. Causes of death were myocardial infarction, brain hemorrhage, and malignant lymphoma of the lungs. Kaplan-Meier plots of probability of graft survival (death with a functioning graft was considered as graft failure) are shown in Figure 1. Probabilities of survival with a functioning graft at 5 years after transplantation (again starting with 100% at 3 months after transplantation) were estimated to be 78% in the CsA group and 87% in the Aza-Pred group (NS). In one patient, a recurrence of focal glomerular sclerosis led to return to dialysis. All other graft failures in surviving patients (eight in the CsA group and three in the Aza-Pred group) were due to rejection.

Rejection episodes. From the time of randomization until the end of follow-up, a total number of 68 rejections were diagnosed in 46 patients. In the CsA group, 43 rejections

TABLE 1. Patient and donor characteristics in 127 study patients who participated in a randomized trial comparing CsA monotherapy with an Aza-Pred combination

	CsA (n=64)	Aza-Pred (n=63)
Data at time of transplantation		
Sex (M/F)	40/24	41/22
Age (yr)	43±13	42±14
Time on dialysis (mo)	30±22	27±17
No. of graft (first/second)	52/12	53/10
Cold ischemia time (hr)	30±7	30±7
Age of donor (yr)	42±16	39±17
Highest % panel reactive antibodies (≤5%/5–85%/≥85%)	25/37/1[a]	30/30/2[a]
No. of mismatches on		
HLA-A (0/≥1)	23/41	33/30
HLA-B (0/≥1)	19/45	38/25[b]
HLA-DR (0/≥1)	46/18	53/10
Prognostic index score[c]		
First transplants	0.87±0.37	0.76±0.36
Second transplants	0.78±0.28	0.48±0.36
Clinical data at time of randomization (3 mo after transplantation)		
Requirement for dialysis after transplantation (%)	22 (34)	15 (24)
Temporary interruption of CsA treatment (%)	14 (22)	12 (19)
One or more acute rejections during first 3 mo (%)	17 (27)	16 (25)
Serum creatinine (μmol/L)	158±60	151±39
Estimated creatinine clearance (ml/min)	55±19	56±19
Proteinuria ≥0.2 g/L (%)	10 (16)	10 (16)
Systolic blood pressure (mmHg)	154±26	153±21
Diastolic blood pressure (mmHg)	92±11	92±8
Use of antihypertensive drug(s) (%)	45 (70)	47 (75)

[a] No data were available for one patient in each group.

[b] $P<0.001$ for difference between the groups.

[c] A higher prognostic index score indicates worse graft prognosis of a first or second graft. The scores for first and second grafts are calculated using different formulas and cannot be compared.

TABLE 2. Course of treatment in 127 patients who were allocated to treatment with CsA monotherapy or Aza-Pred

	Year after transplantation				
	1	2	3	4	5
CsA					
Patients with sufficient length of follow-up[a]	64	62	52	26	8
Patient death/graft failure[b,c]	1/1	2/1	2/5	—/1	—/—
Reasons to deviate from originally assigned therapy[d]					
+Pred					
≥2 Acute rejections	4	—	—	—	—
Chronic rejection	4	3	2	—	—
Other reasons	4	1	1	—	—
CsA → Aza-Pred					
CsA nephrotoxicity	11	2	—	—	—
Other reasons	1	1	—	—	—
+ Aza-Pred					
Chronic rejection and CsA nephrotoxicity	1	1	—	—	—
Immunosuppressive therapy at end of each year					
Continuously on CsA monotherapy	37	28	21	14	4
CsA monotherapy after interruption by other therapy	—	1	1	1	—
Pred	—	1	—	—	—
CsA-Pred	13	13	13	6	3
Aza-Pred	11	10	9	3	1
CsA-Aza-Pred	1	6	1	1	—
Aza-Pred					
Patients with sufficient length of follow-up[a]	63	61	50	28	6
Patient death/graft failure[b]	1/1	2/1	—/—	—/2	—/—
Reasons to deviate from originally assigned therapy[d]					
Aza-Pred → CsA					
≥2 acute rejections	2	1	—	—	—
Bone marrow suppression	8	4	—	—	—
Elevated liver enzymes	4	—	—	—	—
Other reasons	—	1	1	—	—
Immunosuppressive therapy at end of each year					
Continously on Aza-Pred	47	40	35	19	6
Aza-Pred after interruption by other therapy	2	3	3	2	—
CsA	7	6	6	3	—
CsA-Pred	5	9	6	2	—

[a] Patients who died or lost graft function during preceding years were excluded.

[b] The number of patients with a functioning graft at the end of each year equals the number of patients with sufficient length of follow-up minus the number of patients who died or returned to dialysis during that year.

[c] One patient died during the sixth year of follow-up.

[d] Following the deviation of the originally assigned therapy, treatment was changed for a second or third time in some patients (e.g., conversion from CsA to Aza-Pred was sometimes followed by reconversion to CsA-Pred).

occurred in 27 patients (42% incidence of at least one rejection), whereas in the Aza-Pred group 25 rejections were found in 19 patients (30%; NS for difference with CsA). Thirty-five (76%) patients of those with at least one rejection after randomization had no rejection during the first 3 months after transplantation. In the majority of cases, rejections became manifest within 3 months after start of steroid withdrawal or conversion from CsA to Aza randomization (CsA: 19/27, Aza-Pred: 16/19). For rejections occurring between randomization and the end of the first year after transplantation, the interval between randomization and rejection was significantly shorter in the Aza-Pred group (CsA [n=26]: 12±8 weeks, Aza-Pred [n=18]: 6±7 weeks; $P<0.01$). Thus, the incidence of acute rejection within 4 weeks after change of therapy was 3% in the CsA group as compared with 19% in the Aza-Pred group ($P=0.01$). A histologic diagnosis of chronic vascular rejection was made in 17 patients in the CsA group and in 12 cases in the Aza-Pred group (NS). Time from transplantation until the diagnosis of chronic rejection was comparable in both groups (median [range]: CsA, 9 months [4–33]; Aza-Pred, 7 months [4–42]; NS). In all but three CsA-treated and all but four Aza-Pred-treated patients, chronic rejection was preceded by one or more acute rejection episodes.

Patients in whom one or more rejection episodes occurred after allocation to CsA or Aza-Pred treatment did not differ from those without rejections with respect to various clinical and immunological risk factors, prognostic index score, or proportion of patients with rejections in the first 3 months after transplantation. Likewise, the 11 patients in whom rejection ultimately resulted in graft failure were not characterized by extreme levels of HLA mismatches, percentage panel reactive antibodies, or prognostic index score. Remarkably, however, nine of these patients had been free of any rejection episode at the time of conversion or at the start of steroid taper, and in eight of these nine patients, a rejection episode occurred between 4 and 20 weeks after the changes in therapy. Expressed in another way, in patients who had a first rejection episode between 4 and 20 weeks after steroid withdrawal or conversion from CsA to Aza at 3 months after

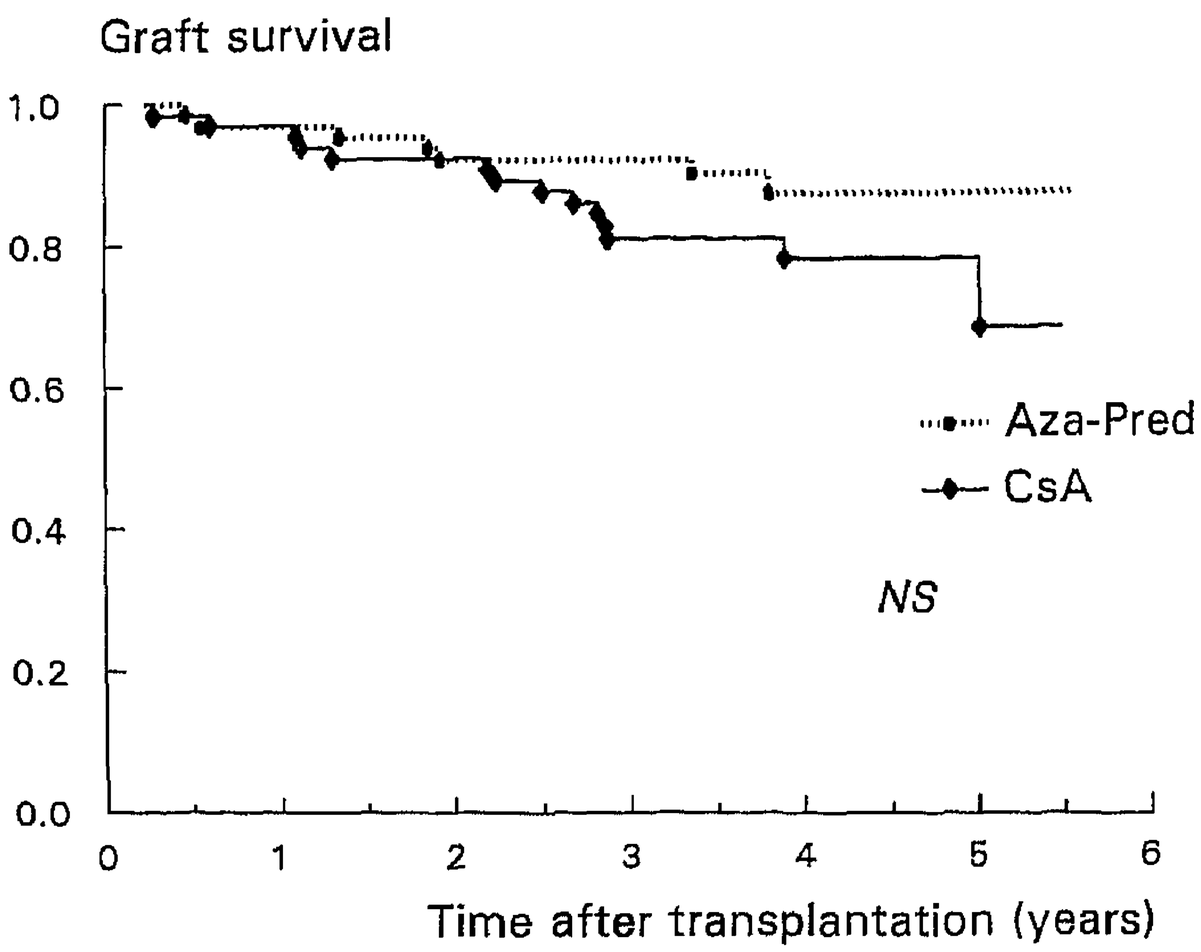

FIGURE 1. Kaplan-Meier graft survival curves of the two treatment groups.

transplantation (n=31), the risk of subsequent graft failure due to rejection was 26%.

When event-free survival was defined as survival with a functioning graft without diagnosis of acute or chronic rejection, the probability of this survival at 5 years after transplantation was estimated to be 48% and 65% in the CsA and Aza-Pred groups, respectively (NS).

Graft function and blood pressure. As expected, conversion from CsA to Aza was followed by a sustained improvement in graft function (Table 3). During the first 3 months after this conversion, the increase in estimated creatinine clearance was 19±20% ($P<0.001$). After withdrawal of steroids in the CsA monotherapy group, a slight increase in serum creatinine was observed. This could not be attributed to the occurrence of rejection, since a rise in creatinine (7.5±13.9% between 3 and 6 months after transplantation, $P<0.01$) was still present after patients with a rejection or overt signs of CsA nephrotoxicity had been excluded. Restricting the comparison between the groups to rejection-free patients who were kept on their originally assigned therapy resulted in 1-year serum creatinine levels of 148±40 μmol/L and 122±30 μmol/l in the CsA and Aza-Pred groups, respectively ($P<0.05$). Except for a transiently lower frequency of proteinuria at 6 months after transplantation in the CsA group, there were no differences in the incidence or degree of proteinuria (latter data not shown). Similar reductions in systolic as well as diastolic blood pressure were observed after withdrawal of steroids or conversion from CsA to Aza (change in systolic blood pressure between 3 and 6 months after transplantation: −6±13% vs. −6±14% [NS], change in diastolic blood pressure: −5±17 vs. −7±12% [NS]). Although diastolic blood pressure tended to be higher in the CsA group, the difference only reached statistical significance at 4 years after transplantation. Antihypertensive therapy was considered necessary in about two thirds of all patients during the first year after transplantation and the requirement for blood pressure reduction did not decline during subsequent years. There was no difference in the need for antihypertensive treatment between both groups.

Infections. During the universally completed follow-up period of 2 years after transplantation, there were no differences between the groups with regard to the number of patients with urinary tract infections, respiratory tract infections, cytomegalovirus infections, or the combined incidence of all other infections.

Cost analysis. Direct treatment-related costs during the first year after transplantation were higher in the CsA group ($P<0.05$, Table 4 and Fig. 2). The majority of data allowed separate analyses for the periods before and after randomization. As expected, there were no significant differences between the groups before randomization. After randomization, the CsA group was characterized by significantly higher drug costs and costs of CsA level measurements. These differences, as well as a tendency to higher costs of hospitalization in the CsA group, mainly accounted for the difference in total whole-year costs. In the CsA group, whole-year costs of CsA comprised 68% of all drug costs, as compared with 48% in the Aza-Pred group. When only the period after randomization was included in the calculations (months 4–12), these figures were 67% and 19% respectively. When costs of standard immunosuppressive therapy (CsA, Aza, and Pred) and of CsA level measurements were not considered, mean costs

TABLE 3. Graft function and blood pressure during follow-up in patients who were allocated to treatment with CsA monotherapy or Aza-Pred from 3 months after renal transplantation[a]

Time after Tx	Serum creatinine (μmol/L)		Proteinuria ≥0.2 g/L (%)		Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		Use of antihypertensive drugs (%)	
	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred
3 Months	158±60	151±39	16	16	154±26	153±21	92±11	92±8	70	75
6 Months	162±46[b]	134±34[c,d]	13	32[e]	142±20[c]	142±20[c]	86±10[b]	85±10[c]	74	64
9 Months	170±49[c]	133±34[c,d]	16	22	145±20	146±22	88±10[f]	87±11[b]	69	62
1 Year	176±69[b]	131±37[c,d]	20	27	144±18[f]	144±22[f]	89±8	86±8[c]	66	66
2 Years	180±78[f]	126±35[c,d]	32	26	142±19[c]	144±20[b]	87±11[f]	86±9[c]	81	74
3 Years	173±78	130±49[c,e]	29	28	146±17[f]	142±23[b]	87±11[f]	84±13[c]	81	71
4 Years	169±64	134±53[b]	35	19	146±19	149±17[f]	89±7	82±9[c,e]	73	78

[a] The numbers of patients with a duration of follow-up of more than 4 years were too small for meaningful comparisons.
[b] $P<0.01$ for differences with baseline values at 3 months after transplantation.
[c] $P<0.001$ for differences with baseline values at 3 months after transplantation.
[d] $P<0.001$ for differences between the CsA and Aza-Pred groups.
[e] $P<0.05$ for differences between the CsA and Aza-Pred groups.
[f] $P<0.05$ for differences with baseline values at three months after transplantation.

TABLE 4. Direct treatment-related costs per patient during the first year after transplantation in patients who were allocated to treatment with CsA monotherapy or Aza-Pred[a]

	CsA	Aza-Pred
A. Hospitalization		
Months 1–3	8,311±4,692	8,036±4,351
Months 4–12	10,520±30,609	5,579±8,925
Entire year	18,831±31,444	13,615±10,159
B. Drugs		
Months 1–3	5,641±2,598	5,829±2,677
Months 4–12	9,064±4,713	4,280±4,062[b]
Entire year	14,706±5,361	10,109±4,680[b]
C. Visits to outpatient clinic		
Months 1–3	816±189	852±185
Months 4–12	1,554±597	1,499±449
Entire year	2,370±625	2,351±502
D. CsA level measurements		
Months 1–3	965±365	1,020±387
Months 4–12	1,009±459	173±347[b]
Entire year	1,975±675	1,194±495[b]
E. Renal replacement therapy		
Months 1–3	551±1,316	374±881
Months 4–12	109±788	35±273
Entire year	660±1,497	409±908
A + B + C + D + E		
Months 1–3	16,285±7,023	16,111±6,674
Months 4–12	22,257±33,727	11,566±11,878[b]
F. Laboratory services (excl. CsA levels)	9,453±7,352	8,516±3,207
G. Other diagnostic and therapeutic activities	4,944±3,882	4,335±4,425
H. Blood products	545±1,168	355±571
Total costs	53,484±44,828	40,882±18,895[c]

[a] When available, separate data are given for months 1 to 3 (i.e., before randomization) and months 4 to 12. Costs are expressed in Dutch guilders. One Dutch guilder is about US $0.60.
[b] $P<0.001$ for differences between the groups.
[c] $P<0.05$ for differences between the groups.

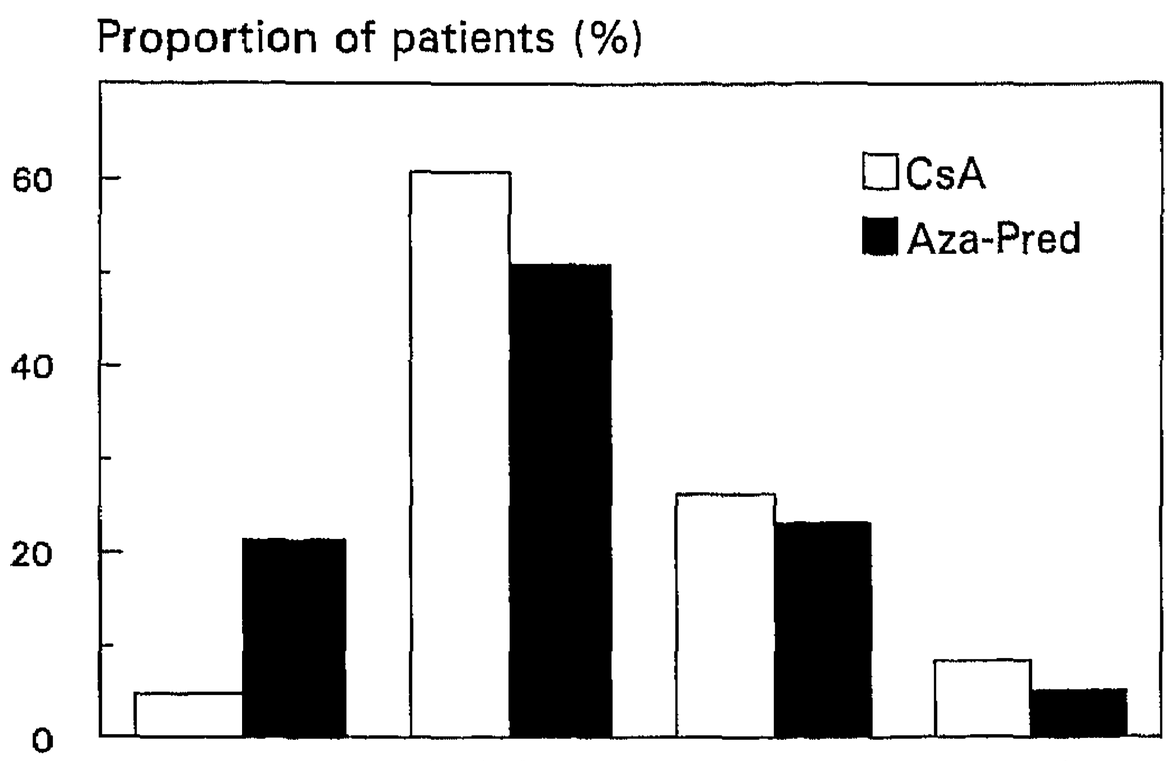

FIGURE 2. Proportion of patients in different categories of total treatment-related costs during the first year after transplantation.

per patient decreased to DFL 41,155±44,890 and DFL 33,655±18,919 in the CsA and Aza-Pred groups, respectively (NS). Exclusion of five patients who were admitted to the intensive care unit (three patients from the CsA group and two from the Aza-Pred group) resulted in a reduction of the mean costs of hospitalization by more than 20%. In the remaining patients, total costs did not significantly differ between the groups (CsA: DFL 44,311±17,159, Aza-Pred: DFL 39,624±17,873). Not surprisingly, in patients who experienced one or more rejection episodes during the first year after transplantation costs were significantly higher than in patients without any rejection (DFL 56,717±39,406 vs. DFL 37,333±26,250; $P<0.001$). Occurrence of a rejection episode after the time of allocation to either treatment group resulted in an increase of total costs by DFL 21,557 per patient in the CsA group and by DFL 17,054 per patient in the Aza-Pred group.

DISCUSSION

This study demonstrates that CsA monotherapy and Aza-Pred treatment from 3 months after renal transplantation are comparably effective immunosuppressive treatment regimens in terms of patient and graft survival. Keeping in mind that survival curves departed from 100% at 3 months after transplantation, the observed patient and graft survival rates agree with the pooled results of other centers using CsA-based immunosuppressive regimens (*20*, *21*). However, the relatively small sample size of the current study may have obscured a difference in graft survival between the groups.

One of our major findings was the rather high incidence of acute rejections after both steroid withdrawal and conversion from CsA to Aza. In several studies the risk of having an acute rejection episode has been shown to decrease with time, and most patients free of rejection at 3 months after transplantation remained so during the rest of the first posttrans-

plantation year (*22*, *23*). In the current study, however, the number of patients with rejections between 3 and 12 months after transplantation exceeded the number of patients with rejections during the first 3 months in both treatment groups. Acute rejections tended to be more frequent in the CsA group but the difference did not reach statistical significance. The 19% incidence of acute rejections within the first month after conversion from CsA to Aza was relatively high as compared with our previous experience of only 6% (*24*). We do not have a clear explanation for this discrepancy since the same treatment schedule, including temporary increase of the prednisone dosage following conversion, was used. With either an overlap between CsA and Aza treatment of at least several weeks or a transient increase in the steroid dosage, other authors reported a rejection incidence during different time intervals following conversion of 15–40% (*11*, *25–28*).

There are several reasons to assume that a considerable proportion of these rejections have been precipitated by the changes in immunosuppressive therapy at 3 months after transplantation. First, the majority of rejections occurred in the first 3 months after change of the therapeutic regimen. In the Aza-Pred group, rejections occurred even earlier than in the CsA group, which may have been caused by the prompt switch of CsA to Aza as opposed to gradual tapering of the steroid dose in the latter group. Second, patients with a rejection following conversion or steroid withdrawal did not differ from nonrejecting subjects with respect to immunological risk factors or incidence of prior rejection episodes, which increases the likelihood of a treatment factor being involved. The low incidence of suboptimal CsA blood levels makes it unlikely that rejections in the CsA group were related to underdosing of this drug. Therefore, elective withdrawal of steroids and replacement of CsA by Aza at 3 months after transplantation seem to increase the risk of rejection, although we could not perform a proper comparison with a control group continued on CsA-Pred. Patients in whom rejection occurred shortly after steroid withdrawal or conversion were particularly prone to subsequent graft failure, which suggests that these reductions in immunosuppressive therapy may have contributed to graft loss in some cases. A higher risk of graft failure in late first-rejection episodes has also been observed by others (*25*).

To our knowledge, only one clinical trial using the same design as the present study has been performed before (*29*). In contrast to our findings, the incidence of rejection episodes in that study tended to be higher in 28 converted patients than in 40 patients who remained on CsA monotherapy (29% vs. 18%). Numerous other studies on elective withdrawal of either CsA or steroids have been published and the results of these studies were reviewed in two recent meta-analyses (*30*, *31*). In accordance with our observations, it was concluded that both steroid withdrawal and discontinuation of CsA increase the risk of acute rejection. Nevertheless, there was no evidence from these meta-analyses that the higher incidence of rejections adversely affects patient or graft survival, although the duration of follow-up of the separate studies may have been too short to detect significant differences.

Although our data are presented as a comparison between CsA monotherapy and Aza-Pred (according to the intention-to-treat principle), the considerable incidence of treatment failures in both groups has to be noticed (Table 2). Resumption of Pred because of acute or chronic rejection and conversion from CsA to Aza-Pred because of CsA-related nephrotoxicity were the main reasons to deviate from the originally assigned CsA monotherapy. At the end of the second year after transplantation, 28 of the 59 patients (47%) with a functioning graft had continuously been kept on CsA monotherapy and a similar rate of protocol adherence has been reported by others (*32*, *33*). Of these 28 patients on CsA monotherapy, 22 had remained free of acute or chronic rejection from the start of steroid taper. Thus, uncomplicated withdrawal of steroids was feasible in about one third of all cases. Return to CsA in the Aza-Pred group became necessary in about 25% of cases, mostly because of Aza-related toxicity.

Graft function was persistently better in Aza-Pred-treated patients. This may be explained in part by the somewhat lower incidence of rejection episodes in this group. Nevertheless, after exclusion of patients in whom a rejection was diagnosed, the difference remained significant. Additional exclusion of patients who did not adhere to their original treatment left some 20% difference in graft function, which probably reflects the magnitude of CsA-induced renal dysfunction. In accordance with recent data from literature (*4*, *5*), we found no evidence for a progressive deterioration of graft function during long-term use of CsA. The interesting observation of a slight decrease in graft function after withdrawal of steroids in CsA-treated patients may mirror the rise in glomerular filtration rate that has been demonstrated in Pred-treated patients with Graves' ophthalmopathy (*34*). Other authors documented an increased incidence of CsA nephrotoxicity in patients treated with CsA monotherapy as compared with those treated with the combination of CsA and Pred (*32*).

Somewhat unexpectedly, there was no substantial difference in blood pressure or use of antihypertensive drugs between groups. As reported before (*35*), there was a considerable reduction in blood pressure following withdrawal of steroids, which equaled that observed after conversion from CsA to Aza. The effect on blood pressure of a daily amount of 10 mg of Pred therefore seems comparable to that of CsA in a dose of 4 mg/kg/day in the population of patients concerned.

In another article, we reported that CsA monotherapy leads to a less favorable serum lipid and lipoprotein profile than Aza-Pred treatment (*15*). Use of CsA was associated with higher concentrations of serum triglycerides and lipoprotein(a), and lower high density lipoprotein cholesterol levels. Contrary to general belief, steroid withdrawal in CsA-treated patients had no beneficial effects on lipid metabolism.

Regarding the important issue of quality of life as an outcome measure after renal transplantation, we observed no major differences between the groups, although a tendency for better scores on psychosocial items was found in patients successfully taken off steroids (*14*).

From an economic point of view, Aza-Pred was the most cost-effective treatment regimen because it coupled lower costs with at least equal efficacy. Higher costs in the CsA group were partly caused by extremely high expenses for hospitalization in a few patients who were admitted to the intensive care unit. Nevertheless, the first-year costs of the drugs composing both immunosuppressive regimens differed by about DFL 4500 per patient when analyzed on an intention-to-treat basis. Previous studies had demonstrated the

cost effectiveness of CsA-containing immunosuppressive regimens (*36*, *37*). However, in these studies control patients did not receive CsA at all, while in the current study all patients were treated with CsA during the first 3 months after transplantation. This initial treatment with CsA protected our patients from the high risk of rejection and associated costs of hospital readmissions during the early phase after transplantation. Indeed, the finding of lower costs associated with the use of CsA in the study of Showstack et al. (*36*) was confined to the direct posttransplantation hospitalization period, while total charges did not differ from those in the control group during the follow-up period. The costs that were related to late rejection episodes in our patients indicate that strategies that reduce the incidence of late rejection episodes may result in important additional savings.

Taken together, we conclude that with regard to graft survival similar results can be achieved with CsA monotherapy and Aza-Pred as intentional treatment strategies from 3 months after transplantation. Most patients benefit from the discontinuation of either CsA or Pred without encountering major problems. While neither regimen differs in its effect on blood pressure, Aza-Pred has the advantages of better graft function, more favorable serum lipid and lipoprotein levels, and lower costs. On the other hand, successful withdrawal of steroid seems superior in terms of quality of life. An important drawback of both withdrawal of steroids and conversion of CsA to Aza, however, is the considerable risk of subsequent rejection episodes. Aside from the chance of irreversible loss of graft function, treatment of these rejection episodes will have to be paid for in terms of a higher incidence of infections, other side effects of the strong immunosuppressive agents that are used, and money (1 course of ATG costs about DFL 5000). Therefore, we believe that the treatment regimens used in this trial are not ideal.

How then to proceed if data indicate that indefinite continuation of both CsA and Pred to reduce the incidence of rejections probably means overtreatment in a substantial number of patients who consequently are exposed to the long-term adverse effects of these drugs? We and others have not been able to identify patients in whom withdrawal of steroids or conversion is likely to be successful (*11*, *35*, *38*). Elective conversion of CsA to Aza at a longer interval after transplantation does not seem to reduce the rejection incidence (*28*, *39*, *40*). Some centers, however, reported quite good results after reduction of immunosuppression in a subgroup of patients characterized by an uneventful course during the first year after transplantation (*41*, *42*). An alternative option is to replace Pred by Aza with continuation of CsA (*35*). The combination of CsA and Aza was recently shown by Opelz (*21*) to provide excellent long-term graft survival rates. Currently we are performing a randomized trial comparing CsA-Pred with CsA-Aza from 6 months after renal transplantation. An important advantage of that trial, as compared with the study described in this article, is the inclusion of a control group of patients who continue on both CsA and Pred. This will allow a better appreciation of the possible occurrence of rejection episodes after replacement of Pred by Aza at 6 months after transplantation.

In summary, CsA monotherapy and Aza-Pred from 3 months after transplantation both resulted in comparable graft survival rates. Either treatment had some advantages in terms of side effects and costs. However, the rather high risk of rejection associated with both regimens requires exploration of other strategies to minimize long-term side effects of CsA and Pred.

Acknowledgments. We thank H. van Lier for statistical advice and help in randomization of the patients. L. Somers of the clinical chemistry laboratory and the staff of the hospital financial administration service (G. van Berlo, Head) are acknowledged for providing data for cost analysis.

REFERENCES

1. Walker RG, d'Apice AJF. Non-specific immunosuppression: azathioprine and steroids. In: Morris PJ, ed. Kidney transplantation. Principles and practice. Philadelphia: Saunders, 1994: 202.
2. Manske CL, Kasiske BL. Lipid abnormalities after renal transplantation. In: Keane WF, ed. Contemporary issues in nephrology, vol 24. Lipids and renal disease. New York: Churchill Livingstone, 1991: 37.
3. Mihatsch MJ, Thiel G, Ryffel B. Histopathology of cyclosporine nephrotoxicity. Transplant Proc 1988; 20: 759.
4. Almond PS, Gillingham KJ, Sibley R, et al. Renal transplant function after ten years of cyclosporine. Transplantation 1992; 53: 316.
5. Burke JFJ, Pirsch JD, Ramos EL, et al. Long-term efficacy and safety of cyclosporine in renal-transplant recipients. N Engl J Med 1994; 331: 358.
6. Curtis JJ. Hypertension following kidney transplantation. Am J Kidney Dis 1994; 23: 471.
7. European Multicentre Trial Group. Cyclosporin in cadaveric renal transplantation: one year follow-up of a multicentre trial. Lancet 1983; 2: 986.
8. Calne RY. Cyclosporin in cadaveric renal transplantation: 5-year follow-up of a multicentre trial. Lancet 1987; 2: 506.
9. Johnson RW, Mallick NP, Bakran A, et al. Cadaver renal transplantation without maintenance steroids. Transplant Proc 1989; 21: 1581.
10. Morris PJ, French ME, Dunnill MS, et al. A controlled trial of cyclosporine in renal transplantation with conversion to azathioprine and prednisolone after three months. Transplantation 1983; 36: 273.
11. Hall BM, Tiller DJ, Hardie I, et al. Comparison of three immunosuppressive regimens in cadaver renal transplantation: long-term cyclosporine, short-term cyclosporine followed by azathioprine and prednisolone, and azathioprine and prednisolone without cyclosporine. N Engl J Med 1988; 318: 1499.
12. van Wezel HB, Hilbrands LB, Koene RA, Hoitsma AJ. Conversion from cyclosporine to azathioprine at 3 months after renal transplantation: long-term results. Transplant Proc 1994; 26: 2550.
13. Hollander AAMJ, van Saase JLCM, Kootte AM, et al. Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. Lancet 1995; 345: 610.
14. Hilbrands LB, Hoitsma AJ, Koene RAP. The effect of immunosuppressive drugs on quality of life after renal transplantation. Transplantation 1995; 59: 1263.
15. Hilbrands LB, Demacker PNM, Hoitsma AJ, Stalenhoef AFH, Koene RAP. The effects of cyclosporine and prednisone on serum lipid and (apo)lipoprotein levels in renal transplant recipients. J Am Soc Nephrol 1995; 5: 2073.
16. Pocock SJ. Methods of randomization. In: Clinical trials. A practical approach. Chichester: John Wiley & Sons, 1983: 66.
17. Thorogood J, van Houwelingen JC, Persijn GG, Zantvoort FA, Schreuder GMTH, van-Rood JJ. Prognostic indices to predict survival of first and second renal allografts. Transplantation 1991; 52: 831.
18. Tiggeler RG, Berden JH, Hoitsma AJ, Koene RA. Prevention of

acute tubular necrosis in cadaveric kidney transplantation by the combined use of mannitol and moderate hydration. Ann Surg 1985; 201: 246.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31.
20. Thorogood J, van Houwelingen JC, van Rood JJ, Zantvoort FA, Schreuder GM, Persijn GG. Factors contributing to long-term kidney graft survival in Eurotransplant. Transplantation 1992; 54: 152.
21. Opelz G. Effect of the maintenance immunosuppressive drug regimen on kidney transplant outcome. Transplantation 1994; 58: 443.
22. Wrenshall LE, Matas AJ, Canafax DM, et al. An increased incidence of late acute rejection episodes in cadaver renal allograft recipients given azathioprine, cyclosporine, and prednisone. Transplantation 1990; 50: 233.
23. Gulanikar AC, MacDonald AS, Sungurtekin U, Belitsky P. The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaver kidney transplants. Transplantation 1992; 53: 323.
24. Hoitsma AJ, Tiggeler RG, Wetzels JF, Berden JH, Koene RA. Cyclosporine treatment with conversion after three months is a safe treatment protocol in renal allograft recipients. Transplant Proc 1988; 20: 161.
25. Shen SY, Weir MR, Coughlin TR. Renal allograft biopsy and conversion of cyclosporine to azathioprine. Transplantation 1989; 47: 223.
26. Helling TS, Wood BC, Nelson PW, et al. Elective conversion from cyclosporine to azathioprine in sensitized patients following cadaveric renal transplantation. Am J Kidney Dis 1990; 15: 137.
27. Delmonico FL, Conti D, Auchincloss HJ, et al. Long-term, low-dose cyclosporine treatment of renal allograft recipients. A randomized trial. Transplantation 1990; 49: 899.
28. Sweny P, Lui SF, Scoble JE, Varghese Z, Fernando ON, Moorhead JF. Conversion of stable renal allografts at one year from cyclosporin A to azathioprine: a randomized controlled study. Transplant Int 1990; 3: 19.
29. Spielberger M, Aigner F, Schmid T, Bosmuller C, Konigsrainer A, Margreiter R. Long-term results of cadaveric renal transplantation after conversion from cyclosporine to azathioprine: a controlled randomized trial. Transplant Proc 1988; 20: 169.
30. Hricik DE, O'Toole MA, Schulak JA, Herson J. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. J Am Soc Nephrol 1993; 4: 1300.
31. Kasiske BL, Heim-Duthoy K, Ma JZ. Elective cyclosporine withdrawal after renal transplantation. A meta-analysis. JAMA 1993; 269: 395.
32. Griffin PJ, Da Costa CA, Salaman JR. A controlled trial of steroids in cyclosporine-treated renal transplant recipients. Transplantation 1987; 43: 505.
33. Sinclair NR. Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. The Canadian Multicentre Transplant Study Group. Can Med Assoc J 1992; 147: 645.
34. van Acker BAC, Prummel MF, Weber JA, Wiersinga WM, Arisz L. Effect of prednisone on renal function in man. Nephron 1993; 65: 254.
35. Kupin W, Venkat KK, Oh HK, Dienst S. Complete replacement of methylprednisolone by azathioprine in cyclosporine-treated primary cadaveric renal transplant recipients. Transplantation 1988; 45: 53.
36. Showstack J, Katz P, Amend W, Salvatierra O. The association of cyclosporine with the 1-year costs of cadaver-donor kidney transplants. JAMA 1990; 264: 1818.
37. Canafax DM, Gruber SA, Chan GL, et al. The pharmacoeconomics of renal transplantation: increased drug costs with decreased hospitalization costs. Pharmacotherapy 1990; 10: 205.
38. Margreiter R, Bosmuller C, Spielberger M, Schmid T, Konigsrainer A. Cyclosporine (Cy) monotherapy after cadaveric renal transplantation. Transplant Proc 1989; 21: 1591.
39. Versluis DJ, Wenting GJ, Derkx FH, Schalekamp MA, Jeekel J, Weimar W. Who should be converted from cyclosporine to conventional immunosuppression in kidney transplantation, and why. Transplantation 1987; 44: 387.
40. Watson MA, Briggs JD, Junor BJ, et al. Randomised trial of conversion from cyclosporin to azathioprine at one year after renal transplantation. Transplant Proc 1989; 21: 1583.
41. Hricik DE, Whalen CC, Lautman J, et al. Withdrawal of steroids after renal transplantation: clinical predictors of outcome. Transplantation 1992; 53: 41.
42. Heim-Duthoy KL, Chitwood KK, Tortorice KL, Massy ZA, Kasiske BL. Elective cyclosporine withdrawal 1 year after renal transplantation. Am J Kidney Dis 1994; 24: 846.

Received 22 June 1995.
Accepted 3 November 1995.